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Introduction

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Over the last 15 years, the principles and practices of cancer treatment have altered more than ever before. These changes have occurred largely as a result of a greater understanding of cancer pathology, the development of sophisticated techniques to aid diagnosis and staging of the disease, and the introduction of new chemotherapeutic agents as well as supportive treatments, including growth factors.

A change in concept

During this time, there has been a change in the concept of disease pathology in cancer. The 'Halstedian Paradigm' has been abandoned in favor of the more modern concept of cancer as a systemic disease, i.e. the 'systemic paradigm'.

The older 'Halstedian Paradigm' centred around two main concepts:

- all tumors are equal in their capacity to metastasize from the primary site, the metastatization depending only upon the tumor size;
- metastatic activity is a two-step process involving the dissemination of tumor cells, first through the lymphatic system to the lymph nodes and secondly from involved lymph nodes, through the blood stream to distant sites in the body.

Unfortunately, the 'Halstedian Paradigm' was responsible for many patients undergoing unnecessary extensive surgery, in the hope that an improved cure rate would be achieved with the largest possible resections. Hopefully, it has now been completely rejected.

The newer 'systemic paradigm' comprises two components:

- a local component which permits diagnosis and staging of the disease; and
- a systemic component not usually visible at diagnosis (micrometastasis) but ultimately responsible for the final prognosis. The probability that such a component would exist is related both to macroscopic characteristics of the primary tumor and to its biological aggressiveness.

If cancer is to be considered as a systemic disease, it is essential that patients receive early systemic treatment with chemotherapy and/or hormonal therapy. Such systemic therapy is now considered to be one of the most critical factors determining disease outcome.

Improved techniques

A more accurate diagnosis of cancer is now possible due to improvements in fine needle aspiration techniques, cytogenetics and molecular biology. More precise staging of the disease is possible using sophisticated imaging techniques, nuclear magnetic resonance, spheroidal computed tomography and immunoscintigraphy. More importantly, it has become possible to determine very precisely the biological profile of the tumor, thus forecasting its natural behavior. This ability to know more about cancer cell biology, on a patient by patient basis, opens the possibility that in the very near future cancer treatment will be adapted to the risk of each patient, thereby avoiding unnecessary toxicity and unjustified economic expense.

The role of cancer chemotherapy

In the last few years, the most important improvements in the treatment of cancer have resulted from the discovery of new drugs. Future advances in oncology will largely depend upon maximizing the

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potential of these new chemotherapeutic agents and therapeutic modalities.

Docetaxel is the first semisynthetic taxoid to undergo clinical development in the US, Canada, Europe and Japan. In clinical studies it has produced particularly promising results in the treatment of several cancers including metastatic breast cancer and non-small cell lung cancer.

It exerts its anticancer effects through the stabilization of tubulin polymerization, and possesses potent antitumor activity *in vitro* against a variety of murine and human cancer cell lines.

In vivo, docetaxel has demonstrated significant activity against a number of murine transplantable solid tumors, including pancreatic, colon and lung carcinomas, and against human tumor xenografts implanted in mice.

Breast cancer

The paper by Martine Piccart presents the very encouraging results obtained with docetaxel in breast cancer, in both first and second lines. More than 300 cases have been summarized, all treated with the standard 100 mg/m^2 Q-3 weeks schedule. The overall response rate in first line was 59% (95% CI: 51–67) with a median duration of response of 8.3 months. Two points are interesting and justify docetaxel being ranked among the most active drugs in the treatment of this disease. First, the response rate obtained was still very high, even in second line, including patients pre-treated and sometimes resistant or refractory to anthracyclines. Secondly, the response rates observed in the liver metastatic site were 54% (first line) and 32% (second line), which is rather unusual compared to the literature with other drugs.

Lung cancer

Thierry Le Chevalier demonstrates that docetaxel is also a very active drug in the treatment of Stage III B and Stage IV non-small cell lung cancer. Among 200 evaluable patients the response rate was 31.3% in 128 previously untreated patients and 19.4% in 72 previously treated patients, with similar response rates in locally advanced and in metastatic diseases. These response rates are comparable or better than those obtained with other single agents.

As for breast cancer, the toxicity was mostly manageable, with an almost systematic alopecia, fatigue, some cases of mucositis, diarrhea, peripheral neuropathy and onychodystrophy. However, it is fluid retention syndrome, present in 20–40% of non-premedicated patients, that may be the limiting factor for repeated long-term administration of docetaxel in some patients.

Its occurrence seems to be related to the total dose and may be improved with the use of prophylactic steroids.

Head and neck and soft tissue sarcomas

One study, reported here by Jaap Verweij, has shown that docetaxel was able to induce a 17% response rate in soft tissue sarcoma with a median duration of response of 5 months. In head and neck cancer, 57 patients were evaluable for response and 35% of them showed a significant response to docetaxel. These results compare favorably with previously published data on single agent activity and may justify further studies considering the use of this drug in first line therapy and in combination with other active drugs such as cisplatinum.

Gastrointestinal cancer

Finally, the paper from Philippe Rougier focuses on gastrointestinal tract cancer, where docetaxel has been shown to have some significant activity in gastric (24% response rate) and pancreatic (20% response rate) cancers but not in colorectal tumors.

However, these studies were rather limited and the results still need to be confirmed on a larger scale. Here as well as in the report from Jaap Verweij the tolerability was mainly acceptable, with fluid retention being a possible long-term limiting side effect in non-premedicated patients.

Conclusion

Docetaxel studies—some limited, as here in pancreatic cancer, and some very large, as here in breast cancer—are numerous, and experience with this new compound is now relatively extensive. The drug is easily administered, is very effective against some important tumors such as breast and non-small cell lung cancer, and can induce durable responses. Its toxicity is very manageable at standard dose and schedule and the frequency of fluid retention episodes, a possible long-term limiting side effect in some patients, seems to improve with the use of corticosteroid pre-medication.